# MCRA 7

a web-based program for Monte Carlo Risk Assessment

# Reference Manual 2010-08-25

documenting MCRA Release 7.0

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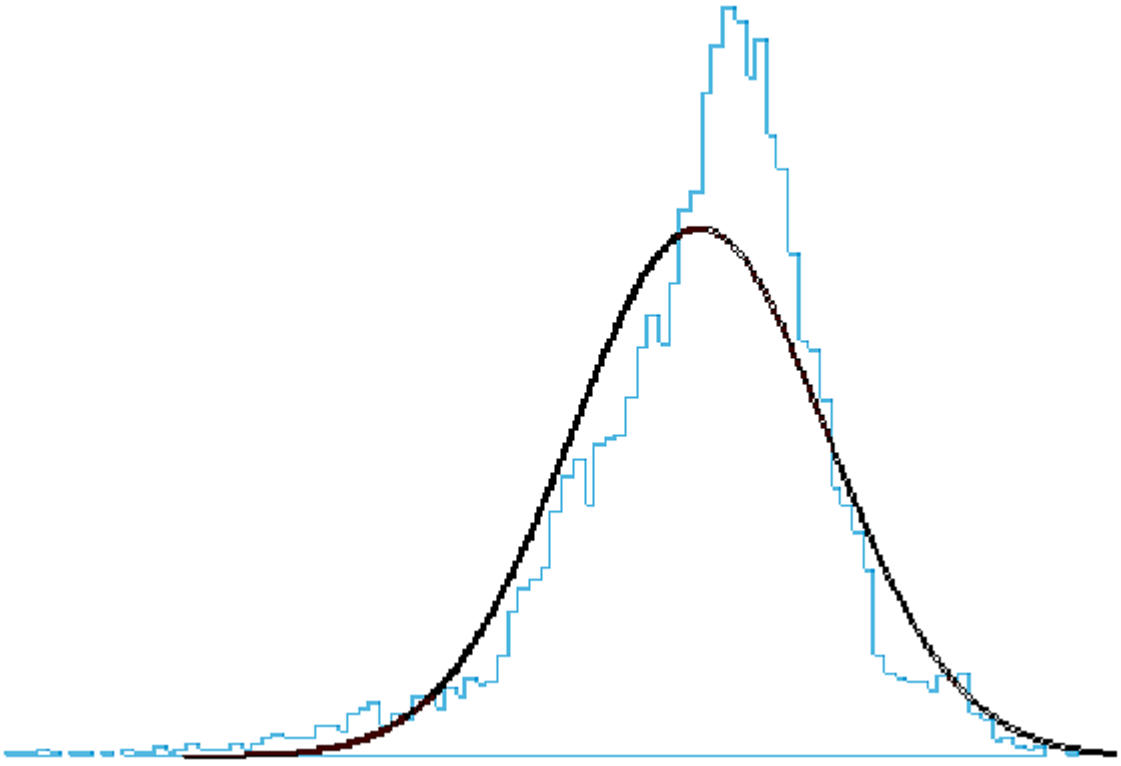

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# 1 Introduction to MCRA

MCRA (Monte Carlo Risk Assessment) is a computational tool for dietary risk assessment of substances in foods based on monitoring data concerning the quality of foods and agricultural products. Intake (exposure) assessment is an important step in risk assessment of substances found in food, such as agricultural chemicals (*e.g.* pesticides, veterinary drugs), toxins (*e.g.* mycotoxins), environmental contaminants (*e.g.* dioxins) and vitamins.

## 1.1 Model description

This manual describes the stochastic (or Monte Carlo) models behind the MCRA program. These models assess acute (short-term) or chronic (long-term) risks due to dietary intake by combining food consumption survey data and concentration data from *e.g.* monitoring programs.

Food consumption data may arise from different sources. Typically, national food consumption surveys or monitoring programs provide information on food intake in the general population. For example, from the Dutch Food Consumption Survey (1997) food consumption patterns ($x_1,...,x_p$), body weight ($w$), age ($a$) and sex ($s$) are available for 6250 individuals on 2 consecutive days. When concentrations are not measured on consumed foods, a composition database is necessary to convert the amounts of food as consumed (*e.g.* pizza) to amounts of foods as measured ($x_1,...,x_p$) which are used in the model. Van Dooren *et al*. (1995) provide such a conversion for the Dutch situation. Concentration data may be available from different sources. In some countries national monitoring databases exist, which are useful for the risk assessment of substances already in use. For example, the Dutch KAP database (van Klaveren 1999) stores annually more than 200,000 records of measurements originating from food monitoring programs for meat, fish, dairy products, vegetables and fruit.

Basically, MCRA simulates daily consumptions by sampling a food consumption database and combines these with a random sample from either a concentration database (empirical distribution) or a parametric distribution of concentrations. The result is a full *distribution* of intakes, rather than traditional deterministic methods which only provide a point estimate. Percentiles of the intake distribution can be used to assess risks by relating them to *e.g.* an acute reference dose (ARfD).

The basic model for the intake of a special substance in an acute risk analysis is:

$$y_{ij} = \frac{\sum_{k=1}^{p} x_{ijk}\ c_{ijk}}{w_i}$$

where $y_{ij}$ is the intake by individual $i$ on day $j$ (in microgram substance per kg body weight), $x_{ijk}$ is the consumption by individual $i$ on day $j$ of food $k$ (in g), $c_{ijk}$ is the concentration of that substance in food $k$ eaten by individual $i$ on day $j$ (in mg/kg, 'ppm'), and $w_i$ is the body weight of individual $i$ (in kg). Finally, $p$ is the number of foods accounted for in the model.
Note that the definition of 'food' is flexible: it may represent a Raw Agricultural Commodity (RAC), *e.g.* 'apple', but it may also specify subdivisions, *e.g.* 'apple, peeled' or 'apple, imported'.

The quantities $x_{ijk}$, $w_i$ and $c_{ijk}$ are assumed to arise from probability distributions describing the variability for food consumption and weight, $p(x_1,...,x_p,w)$, and for concentrations of substances in each food, $p_k(c)$. In principle, these probability distributions may be parametric (*e.g.* completely defined by the specification of some parameter values) or empirical (*e.g.* only implicitly defined by the availability of a representative sample). Given these probability distributions (or estimates thereof) MC-simulations can be used to generate an estimate of the probability distribution $p(y_{ij})$ to assess acute risks by intake of the substance.

In a chronic exposure assessment, the main interest goes to the fraction of individuals with a usual intake per day higher than an intake limit. Usual intake is defined here as the long-run average of daily intakes of a substance by a individual. Usually, food consumption data are available for individuals on 2 (or more) consecutive days. We assume an equal number of days for each individual. This is in confirmity with our method of data entry for consumption. As a consequence, days without consumptions do have zero intake. MCRA calculates the distribution of the usual intakes over individuals based on the average concentration and the empirical distribution of intake between individuals and between different intake days of the same individuals. Percentiles of this usual intake distribution can then be related to *e.g.* the acceptable daily intake (ADI).

The basic model for the intake in a chronic risk analysis is:

$$y_{ij} = \frac{\sum_{k=1}^{p} x_{ijk}\ c_k}{w_i}$$

where $y_{ij}$, $x_{ijk}$ and $w_i$ are defined as before but now concentrations of the substance found in food $k$ enter the model as an average of all values, $c_k$ .

In the MCRA program we have four models available to assess chronic risks:

1) the betabinomial-normal (BBN) model (see 5 ),
2) the logisticnormal-normal (LNN) model (see 6 )
3) the discrete/semi-parametric (ISUF) model without covariable and cofactor (see 7 ).
4) the observed individual means (OIM) model (see 8 )

The models for acute and chronic risks allow for effects of food processing between monitoring and ingestion, they use information on Limit of Reporting (LOR) and percent crop treated to check whether non-detects present a source of uncertainty. For acute risks, unit variability either from available data or using default assumptions can be modelled. Uncertainty of percentiles or intake limits can be established by resampling methods.

Depending on the problem, MC-samples may be drawn from the complete database, from a day- or age-restricted subset or from consumption-days only. In some cases there is insufficient information for specific subgroups in the population. For example, in a study on infants (age up to 12 months), a separately constructed food consumption database has been used (Boon *et al.* 2003).

## 1.2 Data needed

The data needed for MCRA are stored in MS Access databases or Excel. The database format requires a profound understanding about building up a relational database using the primary sources of the data. In exchange, flexibility to pre-process the data is offered and results may be investigated in greater detail. The Excel type of data do have a simple two-way data lay-out. Find in **MCRA 7 Data Formats** a full description of how to prepare the data.
Basically, input data for MCRA originate from two sources: food consumption surveys and monitoring programs on substances found in foods. Often, additional tables are needed to link consumption data to concentration data or to implement model options like unit variability or processing. Figure 1 presents the linkage between tables: consumption data are linked directly to concentration data or in an indirect way, through the use of food composition data, food marketshare data, processing data or by the use of a supertype algorithm.

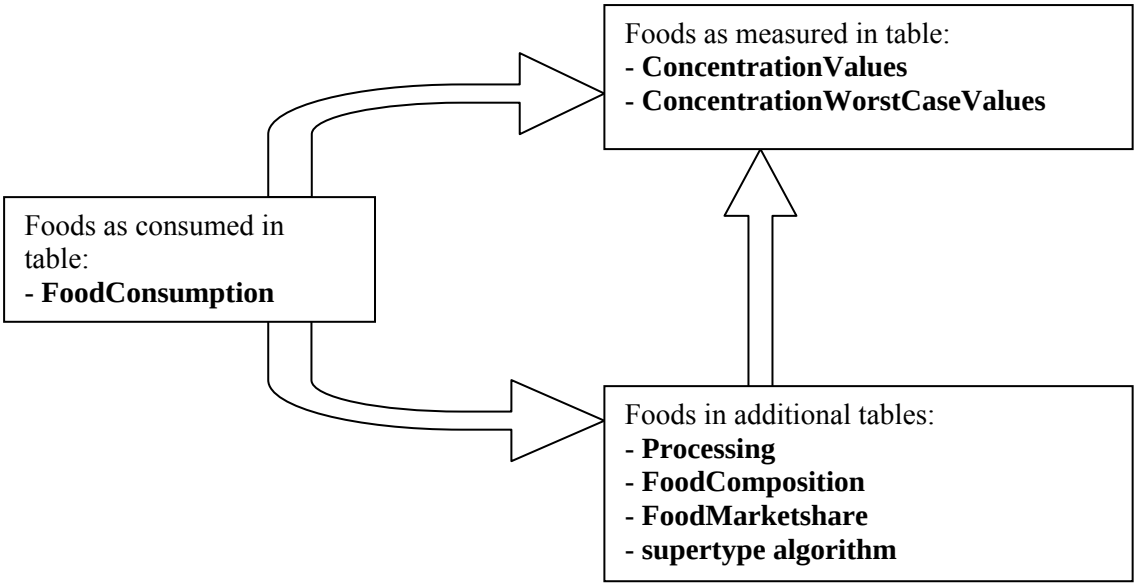



**Figure 1: Links between consumption and concentration data**

Consumption data are consumed portions of food (consumed at different days) of individuals. To get standardized intakes, supply the weight of each individual. Other characteristics of the individuals, like age and/or sex, may be used in further analyses.
Concentration data on substances are the amounts of the substance found on monitoring samples of food.
The category additional tables provide information that links consumption data to concentration data or store information for more sophisticated analyses like unit variability (see Figure 1). Food composition data specifies the composition of foods. So, speaking about pizza, the composition specifies proportions for *e.g.* wheat, tomato, cheese etc. Food marketshare data specifies the proportion of subtypes, so for apple, marketshares are defined for *e.g.* Jonagold, Granny Smith, Golden Delicious etc. Processing data specify the unprocessed food, the processed food and the corresponding processing factors, *e.g.* for grapes raisins are specified. The supertype of a food is, if needed, automatically determined. So the supertype of *e.g.* Granny Smith is apple.

The MCRA system has a central database with example data. However, MCRA is primarily designed to work with user databases, or with a mixture of user and centrally supplied data. For example, provide your own data on concentration levels and combine these with the centrally supplied consumption data. Be careful when combining tables from different databases: codes of foods of centrally supplied data and your own data should be consistent.

## 1.3 Get started

To use MCRA, go to https://mcra.rivm.nl. As a potential new user, first fill in the registration form. After login, the central menu is entered and from here all tasks and corresponding actions are started.

The central menu (Figure 2) contains four main tasks which are described as:

- Data Selection (Access [mdb], Excel [xls] or Simulated Data [xls])
- Specify Model (specification of input options)
- Set and Run (specification of output options, start Monte Carlo Risk Assessment)
- View Output (managing output)


**Figure 2: Central menu**

A main task is started by clicking the button. Then, a menu containing actions related to the main task is displayed. A main button can only be pressed when the name of the tasks is displayed in black. Names of main tasks that are not availabe or active at the moment, are displayed in grey. After clicking a main button, it turns into blue to indicate that the task is active. For a first time user, the figure above shows the central menu and Data Selection can be started (only available option). Otherwise, press New Project to clear all selections.

For a short introduction in MCRA, we refer to **MCRA 7 Examples** or **MCRA 7 Overview**.

# 2 Acute risk assessment

Substance concentrations in the various foods are independent and therefore can be modelled by univariate distributions.

## 2.1 Empirical modeling of concentrations

In the empirical (non-parametric) approach, concentrations are sampled at random from the available data and combined with the consumption data to generate a new distribution of intake values. To assess the risk-intake, percentiles of the intake distribution are estimated.

## 2.2 Parametric modeling of detects and nondetetects

In the parametric approach, concentrations per food are sampled from parametric distributions. A special feature of concentration data is that the large majority of measured concentrations (often more than 80%) is recorded as zero (non-detects). These values may correspond to true zero concentrations (for example because the substance is never used in the specific food), or they may correspond to low concentrations which are below a pre-established Limit of Reporting (LOR).
Regarding all non-detects as censored data values is not always valid. Alternative models exists to fit data that contain non-detects. In [EFSA, draft interim scientific report, 2009], a review is given on the most commonly used statistical methods to deal with non-detects. Among them are substitution, log-probit regression, maximum likelihood estimation and non parametric methods. In the draft EFSA report, the question whether the non-detects are true zero's or low concentrations is not considered, and only described in terms of a combination of more than one log-normal distribution, e.g. binomial and a lognormal.

The lognormal distribution (logarithmic transformed values) with parameters $\mu$ and $\sigma^2$ has been selected as being both theoretically sensible and practically useful (Shimizu & Crow 1988, Van der Voet *et al*. 1999). Based on this priciple, we then have the following six methods:

1. empirical (nLor ≥ 1)
2. mixture of non-detect spike and lognormal (nLor ≥ 1)
3. mixture of non-detect spike and truncated lognormal (nLor = 1)
4. censored lognormal (nLor ≥ 1)
5. censored lognormal with estimated LOR (nLor = 1)
6. mixture of zero spike and censored lognormal (nLor ≥ 1)

with nLor indicating whether multiple values for the LOR are allowed or not.

Additional options for the first three models are:

- if there are non-detect data, these can be replaced by $f$ x LOR for a specified value $f$,
- if $f > 0$, an additional option is to apply percentage crop treated to force true zero concentrations for part of the non-detect data. For legal applications of substances like pesticides, data may be available about the percentage of the crop which receives treatment. When a substance can enter the food chain only via crop treatment, and when the percentage of crop treated is (approximately) known to be $100p_{crop\text{-}treated}$, then this knowledge may be used to infer that $100(1\text{-}p_{crop\text{-}treated})$% of the monitoring measurements should be real zeroes, contributing nothing to intake of the substance, whereas other non-detects in the monitoring data could have any value below the LOR.

For $100(p_{non\text{-}detect} + p_{crop\text{-}treated} - 100)$% of the monitoring measurements, 0 and LOR represent best-case and worst-case estimates. A simple way (tier 1 approach) to consider the uncertainty associated with non-detects is to compare intake distributions for these best-case and worst-case situations.

Method 2 (mixture of non-detect spike and lognormal) can be defended if all positive values are assumed to be above LOR, and P(c<LOR) would be very small for the fitted distribution. It would then be logical to apply $f = 0$ for the nondetects.
Method 3 (mixture of non-detect spike and truncated lognormal) estimates a truncated lognormal distribution. The estimated P(c<LOR) should be lower than the fraction nondetects, and for the difference $f = 0$ would be a logical choice.
Methods 4 (censored lognormal) and 5 (censored lognormal with estimated LOR) assume that there are no true zeroes, which might be a reasonable assumption for many contaminants, though not for artificially added substances. With model 5 the reasonableness of the given LOR value can be checked (assuming the lognormal model).
Method 6 (mixture of zero spike and censored lognormal) fits a mixture distribution, where the nondetects are divided over a spike of true zeroes and the censored tail of the lognormal distribution.
Method 1 (empirical) is the parameter free alternative (default) and samples concentration values directly from the empirical concentration distribution using both detect and nondetect data. It requires to specify a value *f* for the nondetects (also true for methods 2 and 3). This approach requires more data to obtain a satisfying representation of the full distribution.

## 2.3 Estimation

The parameters of the truncated lognormal, censored lognormal and censored lognormal mixture model may be estimated using maximum likelihood. The censored lognormal with estimated LOR is an iterated version of the censored lognormal and searches for the best value of the LOR under the assumption that the observed fraction of non-detects equals the predicted fraction of non-detects. This often improves the fit of the data and supports the notion that values of the LOR are not precisely reported by the analytical labs.

Let $x$ denote a random variable from a lognormal distribution. Then, the log transformed variable $y = \ln(x)$ is normally distributed with mean $\mu_y$ and variance $\sigma_y^2$.
The probability density function (p.d.f.) of $y$ may be expressed as:

$$f_y(y; p_0, \mu_y, \sigma_y^2) = p_0 I(y;0) + \{(1-p_0)(1-I(y;0)\} * \frac{1}{\sqrt{2\pi}\sigma_y} \exp(-\frac{(y-\mu_y)^2}{2\sigma_y^2})$$

where $p_0 = \Pr(y < \log(x_{lor})$ , $x_{lor}$ is the limit of reporting and I($y$;0) is an indicator function for $y < \log(x_{lor})$. For $p_0 = 0$, the p.d.f. of $y$ reduces to the usual lognormal density.

The left truncated density for $y \geq \log(x_{lor})$ equals (assume one LOR):

$$f_y(y; \mu_y, \sigma_y^2) = \frac{1}{\sqrt{2\pi}\sigma_y} \exp(-\frac{(y-\mu_y)^2}{2\sigma_y^2}) / (1 - \Phi(z))$$

with $\Phi(.)$ the standard normal c.d.f. and $z = (\log(x_{lor}) - \mu_y) / \sigma_y$

Model parameters are estimated using maximum likelihood estimation based on the loglikelihood functions specified below:

1) mixture of zero spike and censored lognormal:

$$\log L(p_0, \mu_y, \sigma_y^2) = \sum_{i=1}^{n_0} \log(p_0 + (1-p_0)\Phi(z_i)) + n_1 \log(\frac{1-p_0}{\sqrt{2\pi}\sigma_y}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

4) censored lognormal

When $p_0 = 0$, loglikelihood (1) reduces to

$$\log L(\mu_y, \sigma_y^2) = \sum_{i=1}^{n_0} \log(\Phi(z_i)) + n_1 \log(\frac{1}{\sqrt{2\pi}\sigma_y}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

and for

5) censored lognormal with estimated LOR (assume one LOR)

$$\log L(lor, \mu_y, \sigma_y^2) = n_1 \log(\Phi(z_{lor})) + n_1 \log(\frac{1}{\sqrt{2\pi}\sigma_y}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

3) mixture of non-detect spike and truncated lognormal (assume one LOR)

Ignoring the $n_0$ values below $x_{lor}$ leads to:

$$\log L(\mu_y, \sigma_y^2) = -n_1 \log(1 - \Phi(z)) + n_1 \log(\frac{1}{\sqrt{2\pi}\sigma_y}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

2) mixture of non-detect spike and lognormal

Ignoring the truncated part leads to:

$$\log L(\mu_y, \sigma_y^2) = n_1 \log(\frac{1}{\sqrt{2\pi}\sigma_y}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

where $y_i = \log(x_i)$, $\Phi(.)$ is the standard normal c.d.f., $z = (\log(x_{i,lor}) - \mu_y)/\sigma_y$, $z_{lor} = (\log(lor) - \mu_y)/\sigma_y$, $n_0$ number of censored values ($x_i < x_{i,lor}$), $n_1$ number of uncensored values ($x_i >= x_{i,lor}$) and $x_i$, $i = 1 \ldots n$

The loglikelihood functions are evaluated in R, using the *optim* algorithm to find estimates for $\mu_y$, $\sigma_y^2$ and $p_0$.

In the basic model, for method 1, 2 and 3 we have:

$$c_{ijk} = I_{ijk} \cdot cpos_{ijk}$$

with $I_{ijk}$ indicating whether a concentration is sampled ($I_{ijk}$=1) or not ($I_{ijk}$=0), and $cpos_{ijk}$ is the concentration value according to the chosen method. The probability of $I_{ijk}$ being 1 or 0 depends on the number of detects found for food *k* and $I_{ijk}$ is sampled separately for each individual *i* on occasion *j*.

For method 4 and 5, $p_0 = 0$ and the basic model reduces to:

$$c_{ijk} = cpos_{ijk}$$

For method 6, where $p_0 > 0$, $I_{ijk} = p_0$ and $c_{ijk}$ is sampled as in method 1, 2 and 3.

Occasionally, estimation of the model parameters (mean, variance and zero spike) may fail because concentration data on specific foods are sparse or even missing.

# 3 Processing

Concentrations in the consumed food may be different from concentrations in the food as measured in monitoring programs (typically raw food) due to processing, such as peeling, washing, cooking etc. In general, we assume the model:

$$cpos_{ijk} = f_k \cdot c_{ijk}$$

where $c_{ijk}$ is the concentration in the raw food, and where $f_k$ is a factor for a specific combination $k$ of RAC and processing. Values will typically be between 0 and 1, although occasionally the processing factor may also be >1 (*e.g.* drying as applied for grapes and figs).

The user of the model will have to specify processing factors for each food $k$ as defined in the food consumption data base. For this purpose, it is advised to maintain a data base of processing factors, indexed by substance, RAC and processing type (*e.g.* washing, peeling or other processing). Before running the model, it may then be necessary to specify how the necessary processing factors are derived from the data base entries and/or other information. Example: if there are no processing factors known for captan in pears, it may be decided to use the corresponding factors for apples instead.

Often processing effects may be variable, and this may be entered in the Monte Carlo modeling by specifying two values for each processing factor:

1. $f_{k,nom}$: the nominal value, typically some sort of central value from an experimental study
2. $f_{k,upp}$: an upper 95% confidence limit, which typically will be set by an expert (even if statistical information on variability of the factor is available)

A typical data base entry might thus read:

| RAC | processing | $f_{k,nom}$ | $f_{k,upp}$ |
|---|---|---|---|
| apple | washing | 0.5 | 0.7 |

In the MC-modeling, processing factors can be used in either of three ways (for each food $k$ to be chosen by the user):

## 3.1 No processing factor

Just take $f_k = 1$. This is in most (though not all) cases a worst-case assumption. No data on processing are needed and therefore this route is useful in a first tier approach.

## 3.2 Fixed processing factors

Use $f_k = f_{k,upp}$. Available information on specific processing effects is used, although still in a cautionary way (in accordance with the precautionary principle). Note that $f_{k,nom}$ values need not to be specified. When both are specified, the highest value will be used; worst case scenario.

## 3.3 Distribution based processing factors

Sample $f_k$ using a normal distribution. Log or logit transformed values of $f_{k,nom}$ and $f_{k,upp}$ are used to define the first two moments of the normal distribution. Two situations are distinguished depending on the type of transformation.

a) The logarithms of $f_{k,nom}$ and $f_{k,upp}$ are equated to the mean and the 95% one-sided upper confidence limit of a normal distribution. This normal distribution thus is specified by a mean $\ln(f_{k,nom})$ and a standard deviation $\{\ln(f_{k,upp}) - \ln(f_{k,nom})\}/1.645$. Values are drawn from this distribution in the MC-simulations. Processing factors $f_k$ will be nonnegative. Note: $f_{k,upp}$ and $f_{k,nom}$ values equal to 0 are replaced by a low default value (0.01); this is useful computationally to avoid problems with logarithms.

b) The logits of $f_{k,nom}$ and $f_{k,upp}$ are equated to the mean and the 95% one-sided upper confidence limit of a normal distribution. This normal distribution thus is specified by a mean $\text{logit}(f_{k,nom})$

and a standard deviation {logit($f_{k,upp}$) – logit($f_{k,nom}$)}/1.645. Values are drawn from this distribution in the MC-simulations. Processing factors $f_k$ will be between 0 and 1. Note: $f_{k,upp}$ and $f_{k,nom}$ values equal to 0 and 1 are replaced by default values (0.01 and 0.99); this is useful computationally to avoid problems with logits.

The user should keep in mind that, in case of a lognormal distribution, $f_{k,nom}$ defines the median, while $f_{k,upp}$ quantifies skewness. The same holds for the logistic. Usually, a logarithm will be the standard transformation, but for very skew distributions (see Figure 3) occasionally values above 1 are sampled (upper row, 1rst, 3rd and 5th plot). A logit transformation should be considered instead.

To process simultaneously some foods using fixed factors and others distribution based, choose 'processing (distribution based)'. Now, fixed factors $f_k$ are obtained by providing only $f_{k,upp}$ whereas random factors $f_k$ are sampled when both $f_{k,upp}$ and $f_{k,nom}$ are given.
It is not necessary to fill out a complete list of processing factors for all foods. Missing values of $f_{k,nom}$ and $f_{k,upp}$ are, by default, replaced by the value 1.

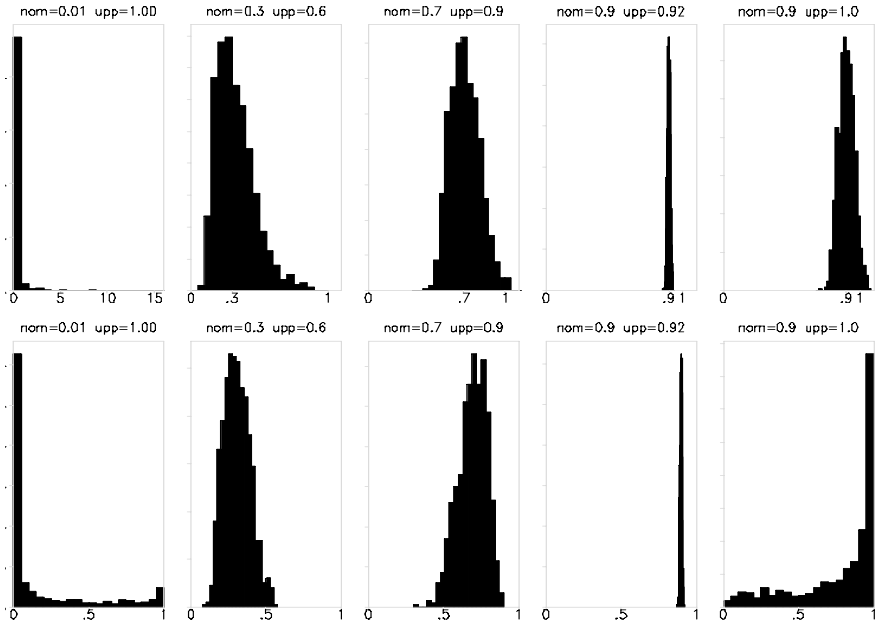



**Figure 3: Lognormal (upper row) and logistic (lower row) distributions for various values of $f_{k,nom}$ (= nom) and $f_{k,upp}$ (= upp)**

# 4 Modeling of unit variability

## 4.1 Variability in composite samples

Variability in concentrations between individual units is a relevant factor in the assessment of short-term dietary intake of substances in food. It is addressed separately because monitoring measurements $cm_k$ are typically made on homogenised composite samples, both in controlled field trials and in food monitoring programs. Such a composite sample for food $k$ is composed of $nu_k$ units with nominal unit weight $wu_k$ each. The weight of a composite sample is therefore $wm_k = nu_k \times wu_k$ . This weight is often larger than a consumer portion, *e.g.* a typical composite sample of 20 sweet peppers weighs 3.2 kg, whereas daily consumer portion weights in the Dutch Food Consumption Survey 1997 ranged from 0.08 g to 458 g.
How should monitoring data be used to estimate the raw food concentration levels $c_{ijk}$ in consumer portions? Although the mean level of $cm_k$ may be a fair estimate of the mean level of $c_{ijk}$, the variability of $cm_k$ is not appropriate to estimate the variability of $c_{ijk}$. In smaller portions more extreme

values may occur more readily, and thus acute risks may be higher than would follow from a direct use of the composite sample data.
Therefore, the FAO/WHO Geneva Consultation recommended to include a *variability factor* (*v*) in the non-probabilistic calculation of an International Estimate of Short Term Intake (*IESTI*) (FAO/WHO 1997). The *IESTI* has been adopted by the Joint Meeting of FAO and WHO experts on Pesticide Compounds in food in 1999, and was modified in 2000 to reflect that the supply for actual consumption on a given day is likely to be derived from a single lot (JMPR 1999, 2000). In both the original and the modified definition, the variability factor is used in a similar way. The basic idea is that the concentration of a substance for the first unit eaten is multiplied by *v*, whereas this factor is not applied for any remaining part of the daily consumption.

In the original presentation *v* was meant to reflect "*the ratio of a highest concentration in the individual product unit to the corresponding concentration seen in the composite sample*" (FAO/WHO 1997). It was not clearly stated what was meant with "*a highest concentration*". Should this be the maximum concentration found or should it be a high percentile, *e.g.* p95 or p97.5? In practical terms this did not matter too much, because little data were available. Therefore the FAO/WHO Consultation recommended to take *initial* values of *v* equal to "*the number of units in the composite sample as given in Codex sampling protocols*". This will provide a conservative estimate of the concentration of the substance in the first unit, based on the assumption that all of the content of the substance present in the composite sample are present in this single unit. If Codex sampling protocols are used, then the number of units per composite sample is 5 for large crops (unit weights > 250 g) and 10 for medium crops (unit weights 25-250 g). For small crops (< 25 g) a variability factor $v = 1$ was recommended. More recently, it has been proposed to replace the default value 10 with 7. For foods which are processed in large batches, *e.g.* juicing, marmalade/jam, sauce/puree, bulking/blending a variability factor $v = 1$ is proposed. To summarise:

| unit weight, *wu* | FAO/WHO default variability factor, *v* |
|---|---|
| < 25 g | 1 |
| 25 –250 g | 7 |
| > 250 g | 5 |
| juicing, marmalade/jam, sauce/puree | 1 |

**Table 1: Default variability factors for IESTI calculations**

The Consultation specifically recommended to replace these default values with more realistic values obtained from studies on actually measured units. A working group of the International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment held in York in 1998 suggested to define *v*, for samples taken from controlled trials, as the 97.5$^{th}$ percentile of the unit levels divided by the sample mean (Harris *et al*. 2000), and this is used in the current version of MCRA as the defining relation.

## 4.2 Deterministic modeling: IESTI

The IESTI is a deterministic estimate of the short-term intake of a substance on the basis of the assumptions of high daily food consumption per individual and highest concentrations from supervised trials. The IESTI is expressed per kg body weight and has only been defined for single foods.

Calculations of IESTI (according to FAO 2002) recognise four different case (1, 2a, 2b and 3). In cases 1 to 3 the following definitions are used:

- LP: Highest large portion reported, calculated as the 97.5$^{th}$ percentile of the distribution of consumed portions on days with positive consumption of the food (kg food/day)
- HR: Highest residue (= concentration ) in composite sample, mg/kg
- bw: Mean body weight, kg; in MCRA values may be input by the user, or weighted means are calculated over individuals with the number of days on which they consumed the food as weights

U: Unit weight of the edible portion, kg.
*v:* Variability factor – the factor applied to the composite value to estimate the concentration in a high-value unit
MR: Median residue (= concentration) in food, mg/kg

Case 1:
The concentration of the substance in a composite sample reflects the concentration in meal-sized portion of the food (unit weight is below 25 gr).

$$\text{IESTI} = \frac{LP * HR}{bw}$$

Case 2:
The meal sized-portion, such as a single fruit or vegetable unit might have a higher concentration than the composite (whole fruit or vegetable unit weight is above 250 gr). Case 2 is further divided into case 2a and 2b.

Case 2a:
Unit edible weight of raw food is less than large portion weight.

$$\text{IESTI} = \frac{U * HR * v + (LP - U) * HR}{bw}$$

The formula is based on the assumption that the first unit contains concentartions at the HR*$v$ level and the next one contains concentrations at the HR level, which represents the concentrations in the composite from the same lot as the first one.

Case 2b:
Unit edible weight of raw food exceeds large portion weight.

$$\text{IESTI} = \frac{LP * HR * v}{bw}$$

The formula is based on the assumption that there is only one consumed unit and it contains concentrations at the HR*$v$ level.

Case 3:
For those processed foods where bulking or blending means that the median represents the likely highest concentration.

$$\text{IESTI} = \frac{LP * MR}{bw}$$

When an acute reference dose is available, the calculated IESTI values are also expressed as a percentage of the ARfD.

## 4.3 Probabilistic modeling: specifying distributions

How should variability between units be incorporated in probabilistic modeling of acute risks? In probabilistic modeling we generate consumption amounts and concentrations which will be multiplied, summed over foods and divided by body weight to estimate the intake. However, the concentration $cm_k$ will usually be derived from a distribution based on measurements on composite samples. Assume that a batch of food contains $N$ units ($N$ large, for the statistics we assume infinite).

The monitoring measurement $cm_k$ is made on a composite sample of $nu_k$ units (for example, $nu_k = 5$). These units are assumed to be representative of the batch. Unit concentrations $c_{ijk}$ are to be simulated for one or more units from this batch that will be part of a consumption portion in the MC-simulation. Basically, there are three possibilities depending on the availability of data:

1. use actual measurement data on individual units;
2. use variability factors or other summary statistics based on measured individual units;
3. use conservative assumptions.

In MCRA only methods under categories 2 and 3 are implemented. The first approach has been pioneered in the context of a large UK survey on pesticides in fruit (Hamey 2000).

The following three models are discussed in more detail:

1. **beta model**, requires knowledge of the number of units in a composite sample, and of the variability between units (realistic or conservative estimates);
2. **bernoulli model**, requires only knowledge of the number of units in a composite sample (results are always conservative);
3. **lognormal model**, requires only knowledge of the variability between units (realistic or conservative estimates).

Preferably realistic estimates of unit variability are to be used, either expressed as coefficients of variation *cv* (standard deviation divided by mean) or as variability factors *v* (defined in MCRA as 97.5$^{th}$ percentile divided by mean). However, often such information is not directly available. In such cases it is customary to select high values for the variability factor, either based on collections of variability factors for other substances/foods, or calculated as the theoretical maximum derived from the number of units in a composite sample.

How to translate the concept of conservatism to the probabilistic model? In a non-probabilistic model a higher value of *v* gives a higher *IESTI*, but in a stochastic model a higher variability means more spread around a central value. In general this means that higher values, but also lower values can be generated. In order to retain an overall conservatism it is therefore necessary to replace all simulated values below the monitoring level ($cm_k$) with $cm_k$ itself.

It is common to use default conservative values, such as the FAO/WHO variability factors in Table 1. However, one should be aware that two entirely different interpretations are possible:

1. The default variability factor may be defined in the same way as a data-based variability factor (*v* = 97.5th percentile/mean). For example, it may be an expert opinion based on seeing many actual data sets from trials, that a certain value v can be used as a conservative value for other situations (see *e.g.* Table 1 in Harris *et al*. 2000). Then we might use the beta or the lognormal model, censoring these distributions at $cm_k$ to guarantee conservative behaviour. For the beta model additional information on the number of units in a composite sample is needed.
2. Alternatively, one can revert to the original definition and interpret FAO/WHO variability factors as the number of units in the composite sample ($v = nu_k$). In this case, without other information, the only workable model is the bernoulli model.

Table 2 describes the four options when a parametric form for unit variability is specified. Measurements are simulated for a new unit in the batch using a lognormal distribution or for a unit belonging to the composite sample leading to the use of the beta distribution.

| | Simulate for new unit in batch<br><br>(lognormal distribution) | Simulate for unit belonging to composite sample<br>(beta distribution) |
|---|---|---|
| Estimates of unit variability are realistic (R) | • no censoring at $cm_k$<br>• no upper limit to the unit concentration | • no censoring at $cm_k$<br>• unit values never higher than $nu_k \cdot cm_k$ |
| Estimates of unit | • unit values will be left-censored | • unit values will be left-censored at |

| | | |
|---|---|---|
| variability are conservative (C) | at $cm_k$<br>• no upper limit to the unit concentration | $cm_k$<br>• unit values never higher than $nu_k \cdot cm_k$ |

**Table 2: Choices for estimated variability factors. $cm_k$ = value of composite sample concentration, $nu_k$ = number of units in composite sample.**

### 4.3.1 Beta model

With this model MCRA will generate values for individual unmeasured units of a measured composite sample. If $cm_k$ is the concentration measured (or simulated) for the composite sample in monitoring for food $k$, then the concentration in any unit can be no larger than $c_{max} = nu_k * cm_k$, where $nu_k$ is the number of units in the composite sample. Under the beta model simulated unit values are drawn from a bounded distribution on the interval (0, $c_{max}$). The parameter for unit variability is specified as a coefficient of variation $cv_k$ or as a variability factor $v_k$ of the unit values in the composite sample.

The standard beta distribution is defined on the interval (0, 1) and is usually characterised by two parameters $a$ and $b$, with $a>0, b>0$ (see *e.g.* Mood *et al.* 1974). Alternatively, it can be parameterised by the mean $\mu = a/(a+b)$ and the variance $\sigma^2 = ab(a+b+1)^{-1}(a+b)^{-2}$, or, as applied in MCRA, by the mean $\mu$ and the squared coefficient of variation $cv^2 = ba^{-1}(a+b+1)^{-1}$. Note that the coefficient of variation is the same for the unscaled and the scaled distributions.

For the simulated unit values in each iteration of the program we require an expected value $cm_k$. This scales down to a mean value $\mu = cm_k/c_{max} = 1/nu_k$ in the (standard) beta distribution. From this value for $\mu$ and an externally specified value for $cv_k$ the parameters $a$ and $b$ of the beta distribution are calculated as:

$$a = b\left(nu_k - 1\right)^{-1}$$

$$b = \frac{\left(nu_k - 1\right)\left(nu_k - 1 - cv_k^2\right)}{nu_k cv_k^2}$$

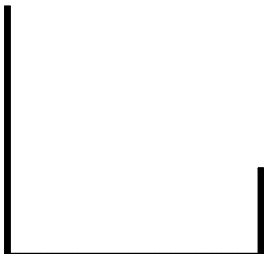
From the second formula it can be seen that $cv_k$ should not be larger than $\sqrt{nu_k - 1}$ in order to avoid negative values for $b$.

When the unit variability is specified by a variability factor $v_k = \frac{p97.5_k}{cm_k}$ instead of a coefficient of variation $cv_k$ then MCRA applies a bisection algorithm to find $a$ such that the cumulative probability $P[Beta(a,b)] = 0.975$ for $b = a\left(nu_k - 1\right)$.

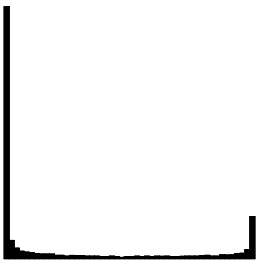
Sampled values from the beta distribution are rescaled by multiplication with $c_{max}$ to unit concentrations $c_{ijk}$ on the interval (0, $c_{max}$).

In the case that variability has been estimated by a conservative high value, all sampled values lower than $cm_k$ are replaced by $cm_k$.

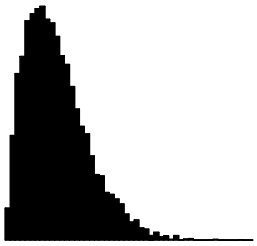
In Figure 4, for several values of the coefficient of variation and number of units the beta distribution is shown with estimated parameters $a$ and $b$. When the parameter for unit variability is high (upper left plot) the ratio of the spikes on the extremes (3:1) represent the 75% probability at $c_{ijk} = cm_k$ and 25% probability at $c_{ijk} = c_{max}$. In the upper right plot, the parameter for unit variability is smaller and some unit values in between the two extremes are sampled. The ratio of the spikes is about 5:1, which is according to the number of units in the composite sample. In the lower left plot, variability is low and unit values are sampled around the monitoring value. In the extreme case, when unit variability is close to zero the monitoring value itself is sampled and a spike occurs (not shown ). The lower right plot shows an intermediate situation, moderate to high variability.



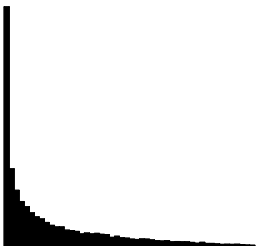
$cv_k$ =1.732; $nu_k$=4; $a$=0.00005; $b$=0.00015



$cv_k$ =1.20; $nu_k$=6; $a$=0.4; $b$=2



$cv_k$=0.62; $nu_k$=6; $a$=2; $b$=10



$cv_k$ =1.46; $nu_k$=4; $a$=0.1; $b$=0.3

**Figure 4: Standard beta distribution for different values of the coefficient of variation $cv_k$ and number of units $nu_k$ in the composite sample. x axis from 0 to 1.**

### 4.3.2 Lognormal model

With the beta and bernoulli models, MCRA simulates concentrations for units in the composite sample, such that the concentration of an individual unit can never be higher than the monitoring measurement multiplied by the number of units in the composite sample $c_{max} = nu_k * cm_k$ .
With the lognormal model for unit variability MCRA simulates concentrations for new units in the batch from which the composite sample was taken. Effectively the number of units in a batch is very large, so in this case there is no practical upper limit to the concentration that can be present.
The lognormal distribution is considered as an appropriate model for many empirical positive concentration distributions. With the lognormal model MCRA assumes a lognormal distribution for unit concentrations. Let this distribution be characterised by $\mu$ and $\sigma$, which are the mean and standard deviation of the log-transformed concentrations. The unit log-concentrations are drawn from a normal distribution with mean $\mu = \ln(cm_{ik})$.

Also for the lognormal model MCRA allows two choices to specify the parameter for the unit variability. The parameter is specified as a coefficient of variation ($cv_k$) or as a variability factor ($v_k$). The coefficient of variation $cv$ is turned into the standard deviation $\sigma$ on the log-transformed scale with:

$$\sigma = \sqrt{\ln(cv^2 + 1)}$$

The conversion of a variability factor into parameters of the lognormal distribution requires an exact definition of what is meant. Here, the variability factor is defined as the 97.5$^{th}$ percentile of the concentration in the individual measurements divided by the corresponding mean concentration seen in the composite sample. A variability factor $v$ is converted into the standard deviation $\sigma$ as follows:

$$v = \frac{p97.5}{mean} = \frac{e^{\mu+1.96\sigma}}{e^{\mu+1/2\sigma^2}} = e^{1.96\sigma-1/2\sigma^2}$$

with $\mu$ and $\sigma$ representing the mean and standard deviation of the log-transformed concentrations. So

$$\ln(v) = 1.96\sigma - 1/2\sigma^2$$

Solving for σ gives: $\sigma^2 - 2*1.96\sigma - 2\log(v) = 0$, with roots for σ according to:

$$\sigma = 1.96 \pm \sqrt{(1.96^2 + 2\log(v))}$$

The smallest positive root is taken as an estimate for σ .

In the case that variability has been estimated by a conservative high value, all sampled values lower than $cm_k$ are replaced by $cm_k$.

### 4.3.3 Bernoulli model

In practice, measurements on individual units to obtain a measure for unit variability are not very common. The bernoulli model is a limiting case of the beta model, which can be used if no information on unit variability is available, but only the number of units in a composite sample is known (see van der Voet *et al*. 2001).

As a worst case approach we may take $cv_k$ as large as possible. When $cv_k$ is equal to the maximum possible value $\sqrt{nu_k - 1}$, the (unstandardised) beta distribution simplifies to a bernoulli distribution with probability $(nu_k - 1)/nu_k$ (or $(v_k\text{-}1)/v_k$) for the value 0 and probability $1/nu_k$ (or $1/v_k$) for the value $c_{max} = nu_k * cm_k$..
In MCRA values 0 are actually replaced by $cm_k$, to keep all values on the conservative side. For example, with $nu_k = 5$, there will be 80% probability at $c_{ijk} = cm_k$ and 20% probability at $c_{ijk} = c_{max.}$.
When the number of units $nu_k$ in the composite sample is missing, the nominal unit weight $wu_k$ is used to calculate the parameter for unit variability.

### 4.3.4 Estimation of intake values using the concept of unit variability

- For each iteration *i* in the MC-simulation, obtain for each food *k* a simulated intake $x_{ik}$ , and a simulated composite sample concentration $cm_{ik}$ .
- Calculate the number of unit intakes $nux_{ik}$ in $x_{ik}$ (round upwards) and set weights $w_{ikl}$ equal to unit weight $wu_k$, except for the last partial intake, which has weight $w_{ikl} = x_{ik} - (nux_{ik} - 1)wu_k$ .
- For the beta or bernoulli distribution: draw $nux_{ik}$ simulated values $bc_{ikl}$ from a beta or bernoulli distribution. Calculate concentration values as $c_{ikl} = bc_{ikl} * cm_{k,\,max} = bc_{ikl} * cm_k * nu_k$. Sum to obtain the simulated concentration in the consumed portion:

$$c_{ik} = \sum_{l=1}^{nux_{ik}} w_{ikl} c_{ikl} \Big/ x_{ik}$$

- For the lognormal distribution: draw $nux_{ik}$ simulated logconcentration values $lc_{ikl}$ from a normal distribution with mean $\mu = \ln(cm_{ik})$ and standard deviation σ. Back transform and sum to obtain the simulated concentration in the consumed portion:

$$c_{ik} = \sum_{l=1}^{nux_{ik}} w_{ikl} e^{lc_{ikl}} \Big/ x_{ik}$$

# 5 Betabinomialnormal model (BBN)

Through the assumed independence of consumption data and concentration values (a most reasonable assumption) the daily intake of individual i on day *j* can be calculated as the aggregated sum over foods of consumption amount per kg body weight times average concentration. For empirical modeling of concentrations, the average concentration of all available concentration measurements on

a food is taken, with non-detect measurements entered as zero, $\frac{1}{2} LOR$ or $LOR$, or any other fraction of $LOR$ as specified in the input options. For parametric modeling of concentrations, the average concentration per food is calculated as:

| model | average concentration for food *k* |
|---|---|
| empirical | $c_k = \frac{1}{n_k}\sum_{i=1}^{n} x_{ik}$ (nondetect $x_{ik}$ may be replaced by $f$ x $LOR$) |
| mixture of non-detect spike and lognormal | $c_k = (1-p_k)\mu_k + p_k(f * LOR_k)$ |
| mixture of non-detect spike and truncated lognormal | $c_k = (1-p_k)\mu_k + p_k(f * LOR_k)$ |
| censored lognormal | $c_k = \mu_k$ |
| censored lognormal with estimated LOR | $c_k = \mu_k$ |
| mixture of zero spike and censored lognormal | $c_k = (1-p_{0k})\mu_k$ |

where $c_k$ is the average concentration (on logscale) for food $k$, $x_{ik}$ concentration value, $\mu_k$ the estimated mean, $p_k$ the fraction of nondetects, $(1-p_k)$, the fraction of detects and $p_{0k,}$ the estimated fraction of true zero's (or true nondetects).

## 5.1 Intake frequency distribution

Let *n* and *npos* be the total number of days per individual (for all individuals equal) and the number of days with a positive intake, respectively. Then *npos* is modelled using a betabinomial distribution with binomial totals *n* and probabilities *p*. The probabilities, *p*, are assumed to follow a beta distribution:

$$f(p) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} p^{\alpha-1}(1-p)^{\beta-1}$$

With $B(\alpha,\beta) = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)}$, the probability that *npos* equals *x* can then be written as:

$$P(\underline{npos}=x) = \binom{n}{x} \frac{B(\alpha+x, n+\beta-x)}{B(\alpha,\beta)}, \qquad x = 0, 1 \ldots n$$

This distribution is known as the betabinomial distribution.

The mean and variance of a beta distribution are:

$\alpha/(\alpha+\beta)$
and $\alpha\beta(\alpha+\beta+n)/[(\alpha+\beta)^2(\alpha+\beta+1)]$, respectively.

Re-parameterizing by $\pi = \alpha/(\alpha+\beta)$ and $\varphi = 1/(\alpha+\beta+1)$ is a more stable and interpretable parameterization. It can be shown that the mean and variance of *npos* are equal to $n\pi$ and $n\pi(1-\pi)[1+(n-1)\varphi]$, respectively.

Note that the first part of the variance $n\pi(1-\pi)$ equals the binomial variance; the second part is the so-called overdispersion factor.

Fitting the betabinomial model with maximum likelihood gives estimates $\hat{\pi}$ and $\hat{\varphi}$ for the parameters $\pi$ and $\varphi$. Back-transformation gives the following estimates for $\alpha$ and $\beta$ :

$$\hat{\alpha} = \hat{\pi}(1-\hat{\varphi})/\hat{\varphi} \text{ and } \hat{\beta} = (1-\hat{\pi})(1-\hat{\varphi})/\hat{\varphi}$$

The distribution of the probability that a individual eats a food with a substance at a certain day is then:

Beta($\hat{\alpha}$ , $\hat{\beta}$ ).

## 5.2 Modeling the positive intake amounts

### 5.2.1 Power or log transformation

First, to achieve a better normality, the positive daily intake amounts are transformed. The user can choose a logarithmic transformation $f(y) = \ln(y)$ (no parameters to be estimated) or a power transformation $f(y) = y^q$ (one parameter to be estimated). In the latter case the optimal power is determined on the grid $\left\{10, 2, 1, \frac{1}{1.5}, \frac{1}{2}, \frac{1}{2.5}, \frac{1}{3}, \frac{1}{3.5}, \ldots, \frac{1}{100}\right\}$, with a further refinement grid search around the best fitting value. If a power $\frac{1}{100}$ gives the best fit in this grid search, then the logarithmic transformation is selected (Note that a logarithmic transform corresponds theoretically to $q = 0$). The goodness of fit is determined by minimising the residual sum of squares: $(z(i) - \beta_1 y^q)^2$ of a regression of normal Blom scores on the power-transformed daily intakes. Normal Blom scores are (Tukey 1962):

$$z_{(i)} = \Phi^{-1}\left(\frac{i - \frac{3}{8}}{n + \frac{1}{4}}\right)$$

where $i$ is the rank of the $n^{th}$ non-zero daily intake, $n$, the total number of non-zero intakes and $\Phi^{-1}(\cdot)$ is the inverse of the standard normal cumulative distribution function.

### 5.2.2 Model with between-individual and within-individual variance component

The transformed positive intake amounts are modelled in a ML analysis with random terms *individual* and interaction *individual.day* to estimate the between-individual and within-individual variance component. For a logarithmic transformation :

$$\ln(\underline{y}_{ij}) = \mu + \underline{c}_i + \underline{u}_{ij}$$

and a power transdormation (with power $q$)

$$\underline{y}_{ij}^{\,q} = \mu + \underline{c}_i + \underline{u}_{ij}$$

where $\underline{c}_i$ and $\underline{u}_{ij}$ are the individual effect and interaction effect, respectively. These effects are assumed to be normally distributed N(0, $\sigma^2_{between}$) resp. N(0, $\sigma^2_{within}$).

If the positive intake amounts are logarithmically transformed it can be shown that the expectation and variance of the positive intake amount per random consumption day of a random individual are:

$$E(\underline{y}_{ij}) = \exp(\mu + \tfrac{1}{2}\,\sigma^2_{within})$$

$$Var(\underline{y}_{ij}) = \sigma^2_{between}$$

For the power transform the expectation equals:

$E(\underline{y}_{ij}) = \mu^{\lambda} + \frac{1}{2}\lambda(\lambda-1)\mu^{\lambda-2}\sigma^2_{within}$ (Dodd *et al.,* 2006)

## 5.3 Modeling usual daily intake

### 5.3.1 Analytical integration

For logarithmic transformed intake amounts, a analytical solution is available (not implemented in the MCRA program).
The usual intake is defined as the intake amount per random intake day (over both intake and non-intake days) of a random individual. To obtain the usual intake the $E(\underline{y})$ from 5.2.2 has to be multiplied by the probability $\pi$ from 5.1 . If $\pi$ was constant for all individuals the usual intake would have a lognormal distribution with mean $\ln(\pi) + \mu + ½\ \sigma^2_{within}$ and variance $\sigma^2_{between}$. But because we have assumed in 5.1 that individuals have different $p$'s coming from a beta distribution, the probability that a individual has a usual intake lower than say an intake limit $z$ equals:

$$P(py \le z) = \int_p (\underline{p} = p \wedge \underline{y} \le \frac{z}{p}) = \int_p (\underline{p} = p \wedge \ln \underline{y} \le (\ln(z) - \ln(p)))$$

$$\int_{p=0}^{1} \frac{\Gamma(\hat{\alpha}+\hat{\beta})}{\Gamma(\hat{\alpha})\Gamma(\hat{\beta})} p^{\hat{\alpha}-1}(1-p)^{\hat{\beta}-1}\Phi\left(\frac{\ln(z) - \ln(p) - \hat{\mu} - ½\,\hat{\sigma}^2_{within}}{\hat{\sigma}_{between}}\right) dp$$

where $\Phi$ is the cumulative normal distribution.

### 5.3.2 Numerical integration

If the positive amounts are transformed by a power transformation the power transformed values can not generally be written in terms of a probability distribution as in 5.3.1 : the distribution of the usual intakes has to be calculated numerically.
However, in the MCRA program for both power and logaritmic transformation, the usual intake distribution is obtained by numerical integration.
The distribution of the usual intakes can be obtained as follows:

1. Draw 1 value of a normal distribution with mean $\mu$ and variance $\sigma^2_{between}$
2. Calculate the inverse transformation of the value of Step 1.

   2a. For a logarithmic transformation: $x = \exp(\mu + \sigma_{between}\ ln\ y) + ½\ \sigma^2_{within}$.

   2b. For a power transformation: $x = (\mu + \sigma_{between}\ e)^{\lambda} + \lambda(\lambda - 1)\ (\mu + \sigma_{between}\ e)^{\lambda-2}\ \sigma^2_{within}/2$

   with $q = 1/\lambda$, the power to approximately normality, $e$ standard normal distributed N(0, 1) (Dodd *et al*. 2006, p1646).

3. Draw 1 value of the beta distribution
4. Multiply the value of Step 2. with the value of Step 3.

The result is one random draw from the distribution of usual intakes.
Repeat Steps 1 till 4 a great number of times, say 50000.

### 5.3.3 Extending the models

The intake frequency and transformed intake amount model can be extended to describe the effect of a covariable and/or cofactor. Then, usual intakes are dependent on explanatory variables.

For frequencies:

cofactor: $\text{logit}(\underline{\pi}) = \beta_{0l}$

covariable: $\text{logit}(\underline{\pi}) = \beta_0 + \beta_1 f(x_1; df)$

both: $\text{logit}(\underline{\pi}) = \beta_{0l} + \beta_1 f(x_1; df)$

Interaction: $\text{logit}(\underline{\pi}) = \beta_{0l} + \beta_{1l} f(x_1; df)$

For amounts

cofactor: $\text{transf}(\underline{y_{ij}}) = \beta_{0l} + \underline{c_i} + \underline{u_{ij}}$

covariable: $\text{transf}(\underline{y_{ij}}) = \beta_0 + \beta_1 f(x_1; df) + \underline{c_i} + \underline{u_{ij}}$

both: $\text{transf}(\underline{y_{ij}}) = \beta_{0l} + \beta_1 f(x_1; df) + \underline{c_i} + \underline{u_{ij}}$

interaction: $\text{transf}(\underline{y_{ij}}) = \beta_{0l} + \beta_{1l} f(x_1; df) + \underline{c_i} + \underline{u_{ij}}$

where l=1…$L$ and $L$ is the number of levels of the cofactor, $\underline{y_{ij}}$ , the amount, $x_1$ is the covariable, f is a spline or polynomial function, df the degrees of freedom, $\underline{c_i}$ and $\underline{u_{ij}}$ are the individual effect and interaction effect respectively. These effects are assumed to be normally distributed N(0, $\sigma^2_{between}$) resp. N(0, $\sigma^2_{within}$). The degree of the function is determined by backward or forward selection.

The usual intake is calculated for the combination of all levels of the cofactor and a specified number of values of the covariable.

# 6 Logisticnormalnormal model (LNN)

Daily intakes are calculated as described in section 5 . In the BBN model, frequencies are modelled using a betabinomial distribution. In the logisticnormalnormal (LNN) model, the betabinomial part is replaced by a logistic regression transforming the data to normality using the logit transform and modeling the individual effects as a random term. The amounts are transformed and modelled as described by the BBN model.

In notation, for probability $p$:

$$\text{logit}(p) = \log(p/1\text{-}p) = \mu_i + \underline{c_i}$$

where $\mu_i$ represents the person specific fixed effect model and $\underline{c_i}$ represent person specific random effects with estimated variance component $\sigma^2_{between}$.

# 7 Discrete/semi-parametric model (ISUF)

Nusser *et al.* (1996) describe how to assess chronic risks for data sets with positive intakes (a small fraction of zero intakes was allowed, but then replaced by a small positive value). The modeling allowed for heterogeneity of variance, *e.g.* the concept that some people are more variable than others with respect to their consumption habits. However, a disadvantage of the method was the restricted use to contaminated foods which were consumed on an almost daily basis, *e.g.* dioxin in fish, meat or diary products. The estimation of usual intake from data sets with a substantial amount of zero intakes became feasible by modeling separately zero intake on part or all of the days via the estimation of intake probabilities as detailed in Nusser *et al.* (1997) and Dodd (1996). In MCRA, a discrete/semi-parametric model is implemented allowing for zero intake and heterogeneity of variance following the basic ideas of Nusser *et al.* (1996, 1997) and Dodd (1996).

Nusser *et al.* (1996, 1997) describe a procedure for the assessment of chronic risks using non-normal dietary intake data. Principally, their method consists of four steps:

1. transforming the daily intake data to approximate normality using a power function or log transformation
2. fitting a grafted polynomial function to the power or log transformed daily intakes. The polynomial provides some flexibility against power transformed components that are still deviating from normality,
3. estimating the parameters of the usual intake distribution in the transformed scale, and
1. estimating the percentiles of the distribution of usual intakes in the original scale.

## 7.1 Power or log transformation

Daily intakes are calculated as described in section 5 . First, to achieve a better normality, the positive daily intake amounts are transformed. The user can choose a logarithmic transformation $f(y) = \ln(y)$ (no parameters to be estimated) or a power transformation $f(y) = y^q$ (one parameter to be estimated).

## 7.2 Spline fit

To achieve a better normality, a second transformation (optional) is performed: a spline function $t = g(z)$ is fitted to the logarithmically or power transformed data *t* as a function of the normal Blom scores. The spline function is a grafted polynomial consisting of cubic polynomials between $p = 3$ joint points (knots) and linear functions in the two outer regions. The daily intakes are transformed by interpolating from *t* to $x = g^{-1}(t)$, using the fitted spline function.

After a successful transformation the daily intakes *x* will resemble Blom normal scores and their mean and total variance will therefore be approximately 0 and 1. The normality of the transformed values *x* is checked with the Anderson-Darling test. In the case of a spline transformation, if normality is rejected at the 85% confidence level, then the number of knots *p* is increased and the spline fit is repeated (until a maximum of 22 knots).

## 7.3 Estimation of the parameters of the usual intake distribution

Variance components for between and within-individual information are fitted to the transformed non-zero daily intakes *x* using the model:

$$x_{ij} = x_i + u_{ij}$$

$$x_i \sim N(\mu, \sigma_B^2); \quad u_{ij} \sim N(0, s_i^2); \quad E(s_i^2) = \sigma_0^2; \quad \text{var}(s_i^2) = \sigma_A^2$$

In this model the total variance of the daily intakes is divided into a between-individual component and a within-individual component. The within-individual variance component can be heterogeneous, that is, it can be different for different individuals. In the model the between-individual variance $\sigma_1^2$ and the mean and the variance of the within-individual variance component distribution ($\sigma_B^2$ and $\sigma_A^2$) are estimated using standard statistical methods (ANOVA). Further, a test statistic *MA4* is calculated to test whether the heterogeneity of variances is significant (see Dodd 1996 for details). The estimate $s_B^2$ of the between-individual variance is the basis for the estimation of the distribution of usual intake. The distribution of usual intakes on non-zero intake days in the *x* scale is represented by a set of 400 normal Blom scores (which themselves represent the standard normal distribution) multiplied by $s_1$: $x_i = s_B z_{(i)}$. The same calculation is applied to user-requested percentiles $z_p = \Phi^{-1}(p)$.

## 7.4 Back transformation and estimation of usual intake

The 400+ values $x_i$ are back-transformed to the original scale. This is simple if no spline function has been estimated. If a spline function has been used, then it is a rather complicated procedure, because the spline function $g$ was developed for daily intakes, not usual intakes. The following steps are made:

1. First the 400+ values $x_i$ are expanded in a set of 9 * 400 values representing the distribution of daily intakes around each of the 400 points;
2. These 9 * 400+ values are back transformed using the functions $g$ and $f$, and the sets of 9 values are then recombined (by weighted averaging) into 400 usual intake values $y_i$ ;
3. A spline function $g_1$ ,especially adapted for usual intakes, is now fitted to the 400 data pairs ($x_i$, $t_i$), where $t_i = f(y_i)$;
4. Finally the usual intakes on non-zero intake days are represented by the back-transform using this improved function: $y_i = f(g_1(x_i))$.

The user-requested percentiles $y_p$ are the additional values ($i$ > 400) in the 400+ set. The 400 $y_i$ values define the cumulative distribution function by:

$$F(y_i) = \frac{i - \frac{3}{8}}{400 + \frac{1}{4}}.$$

The distribution is adapted in order to account for days with zero intake of individuals (defined here as individuals who have a positive probability of intake on any day, and therefore a non-zero usual intake). This is done by estimating the distribution of individual intake probabilities. This distribution is approximated via a number of classes (*e.g.* 21 or 51, can be selected by the user) arranged by the proportion of days on which there is a positive intake ($p_m$). Using a binomial distribution for each class, the fraction of individuals in each class ($\theta_m$; $m = 0,...,M$ ) is estimated by optimising the fit of the predicted proportions of individuals with 0, 1, 2, ... intake days to the observed proportions. The number of parameters to be estimated is usually higher than the number of possible outcomes for a individual (*e.g.* 3 when there are two days per individual), and therefore a smooth approximation is made using a modified minimum chi-squared estimator. See Dodd (1996) for details. Only the fraction of non-consumers ($\theta_0$) is estimated separately with no restriction to be similar to the other $\theta_m$. It can be noted that the distribution of individual intake probabilities can be better estimated when the number of days per individual in the consumption survey becomes higher. With only 2 days per individual the procedure gives a rather artificial distribution, often with an estimated $\theta_0$ of zero This step can be time-consuming. Therefore, the number of iterations in the estimation procedure can be limited by the user. In our experience it is not generally necessary to use 50,000 iterations as in Dodd (1996).

The estimated distribution of individual intake probabilities ($\hat{\theta}_0,...,\hat{\theta}_M$ ) is used to transform the distribution of usual intake on non-zero intake days ($F_y$) to the distribution of usual intake for individuals ($F_C$) and finally to the distribution of usual intake for the entire population ($F_U$). These transformations are based on the relation:

$$F_U(u) = \theta_0 + \sum_{m=1}^{M} \theta_m F_y(u/p_m)$$

which basically says that to obtain a certain level of usual intake $u$ we should consider a different level ($u/p_m$) for the class of individuals which consume only on a fraction $p_m$ of days. See Dodd (1996) for details of the computational procedure. Linear interpolation based on the 400 values of the $F_y$ distribution is then used to compute representations of the cumulative distribution functions for individuals only and the entire population.

# 8 Observed individual means (OIM)

The usual intake distribution for a population is estimated with the empirical distribution of within-individual means. Each mean is the average of all single-day intakes (see 5 ) for an individual. The mean value for an individual still contains a considerable amount of within-individual variation. As a consequence, the distribution of within-individual means has larger variance than the true usual intake distribution and estimates using the OIM-method are biased, leading to a too high estimate of the fraction of the population with a usual intake above some standard.

# 9 Acute risk assessment and the BBN model

An acute risk assessment may be followed by an analysis where the acute intake distribution is related to a covariable and/or cofactor. Through MC-sampling, a large number of intakes is generated by combining randomly chosen consumption patterns of individuals *i* on day *j* with randomly chosen concentrations in the consumed foods. The replicates generated for individual day *ij* are further indexed by *k* to represent differences due to concentration variability. We ignore the finiteness of the concentration data, that is, we ignore the identity of the chosen concentration values in the original concentration dataset.

## 9.1 Intake frequency model

Let $n_i$ and $npos_i$ be the total number of simulated intakes per individual, and the number of simulated positive intakes, respectively. Then $npos_i$ is modelled as a function of *e.g.* age (and/or other individual characteristics), using a betabinomial distribution with binomial totals $n_i$ and overdispersion parameter $\phi$ (independent of age). The fitted binomial probabilities are $\hat{\pi}_x = f(x_i)$, where $x_i$ is the age of individual *i*, and the estimated overdispersion parameter is $\hat{\phi}$.

## 9.2 Intake amount model

For the positive intakes, consider power of logarithmically transformed values $y_{ijk}$. (see 5.2.1 ) Average over replicates to obtain individual day averages $y_{ij.}$. These values are modelled in a ML analysis with random terms individual and individual.day as a function of age (and/or other individual characteristics), with the number of values per individual day ($n_{ij}$) as weights $w_{ij}$ to correct for differences in the precision at the individual day stratum. The fitted values from the model are $\hat{\mu}_x = f(x_i)$, where $x_i$ is the age of individual *i*

## 9.3 Estimating the acute risk variability of positive intake amounts

Correct the full set of simulated positive intakes by $y'_{ijk} = y_{ijk} - \hat{\mu}_{x(i)}$. Estimate the variance $\sigma^2_{y'}$ of $y'_{ijk}$. We denote the estimated variance as $\hat{\sigma}^2_{y'}$. Now for each selected age *x* the transformed positive intake distribution is modelled as normal with mean $\hat{\mu}_x = f(x)$ and variance $\hat{\sigma}^2_{y'}$.

## 9.4 Estimating the acute intake distribution

Acute intake distributions dependent on a covariate are obtained by numerical integration. For each combination of levels of the covariable and cofactor, intake frequency values and transformed intake amounts are simulated and multiplied. This results in a number of distributions each one representing the acute intake distribution corresponding to a specific combination of levels of the covariates.

# 10 Brandloyalty and marketshares

Different brands of a food product may differ in levels of chemical substances or contaminants. For example, brands of potato crisps may have different levels of acrylamide due to differences in the sugar content of used potato varieties or differences in baking procedure (temperature, baking time). If both consumption data and concentration data are measured at the brand level, this presents no special difficulties for exposure assessment. Each brand is then just treated as a separate product. However, in practice brand information is often available for the concentration data, but not for the consumption data. In such cases it is necessary to have additional information on the consumption of the different brands.

For a certain type of product, market share data are often available specifying the percentages of each brand. Ideally these percentages are weight percentages, but sales percentages may be used as a proxy.

## 10.1 Acute health effects

For acute health effects market shares are all that is needed to adapt a probabilistic exposure assessment. For each simulated consumption a brand can be selected with a probability proportional to the market share, and then a concentration value can be sampled from the distribution of concentrations specific for that brand.

## 10.2 Chronic health effects

In the case of chronic health effects we need additional information. It now becomes important to know if individuals always consume the same brand, or that they consume different brands, thus effectively averaging the concentrations of the different brands in their long-term food intake. The tendency to repurchase the same brand has become known as *brand loyalty*.

There are two main approaches for modeling brand loyalty, known as the stochastic and deterministic approach (Odin *et al*. 2001). Whereas the stochastic approach just tries to give a satisfying description of observed brand loyalty behaviour, the deterministic approach tries to analyse the attitude of individuals towards brand selection in terms of a limited number of explanatory factors. In the context of dietary risk assessment it is typically the stochastic approach which is more useful.

There is a simple stochastic model which has turned out to be extremely useful in analysing buying behaviour. This is the socalled *Dirichlet* model, first given in a comprehensive form by Goodhardt *et al.* (1984). The surprising feature of this model is that it contains only one parameter for brand loyalty, implying that brand loyalty varies little, or relatively little, between competitive brands (Ehrenberg *et al*. 2004). Although this may seem a too simple representation at first, it has been found to give a close description of actual buyer behaviour in most cases of a systematic check across 34 products categories (Uncles *et al.* 1994).

## 10.3 The Dirichlet model adapted for probabilistic exposure assessment

In a probabilistic model for chronic exposure asessment when brands are known for concentration data, but not for consumption data, we need the following information:

1. the distribution of consumption by individuals on multiple days;
2. for each brand: the distribution of concentrations in that brand of product;
3. market shares of all brands of a product, and a brand loyalty factor L.

Typically 1 and 2 will be in the form of empirical datasets, for example resulting from food consumption surveys and monitoring programmes, respectively. Alternatively, we can specify parametric distributions, with parameters that are fitted to data or just specified based on prior knowledge or assumptions in what-if scenarios.

Technically the Dirichlet model for brand choice needs *nbrand* parameters $\alpha_i$ (which should be positive real numbers). The average brand choice probability for each brand is $\alpha_i/S$, where $S = \sum \alpha_i$ . By definition, the market shares $m_i$ should be proportional to the brand choice probabilities, and thus to the parameters $\alpha_i$. This means that S, the sum of the alphas, is the only

additional parameter that should be specified, and indeed this is the parameter that determines brand loyalty. S=0 corresponds to absolute brand loyalty, and brand loyalty decreases with increasing S. We define $L = (1+S)^{-1}$ as an interpretable brand loyalty parameter, where now $L = 0$ and $L = 1$ correspond to the situations of no brand loyalty and absolute brand loyalty, respectively.

Given empirical or parametric distributions of consumption and concentration values, the algorithm for chronic exposure assessment now operates as follows:

1. collect consumptions for a large number of $n$ of individuals,
2. in case of market shares: simulate $n$ selection probabilities from the Dirichlet distribution,
3. estimate intake $y_{ijk}$ for individual $i$ on day $j$ for food $k$ as the weighted sum of the average concentration for $B$ brands times consumption $x_{ijk}$ and standardize for body weight. In notation: $y_{ijk} = \frac{\sum_{b=1}^{B} x_{ijk} c_{kb} bcp_{ikb}}{w_i}$, where weight $bcp_{ikb}$ is the brand choice probability $b$ for food $k$ of individual $i$, $c_{kb}$ is the average concentration for brand $b$ of food $k$. Note that $\sum_{b=1}^{B} bcp_{ikb}$ sums to 1 for each individual $i$,
4. aggregate intakes over the number of foods $p$,
5. proceed as usual

# 11 Uncertainty analysis: resampling data sets and resampling from distributions

In probabilistic risk assessment of dietary intake we use distributions which describe the *variability* in consumption within a given population of individuals and the *variability* of the occurrence and level of substances in the consumed foods. However, these calculations do not consider the amount of *uncertainty* that is due to the limited size of the underlying datasets. Typically, in a large number of simulations very many different combinations of consumption and concentrations are made. This leads to a smooth distribution of simulated intakes, and the impression of a very precise estimation of intake percentiles or other quantities of interest. It is essential to realise that the accuracy of the inference depends on the accuracy of the basic data.

When doing an uncertainty analysis in MCRA a number of iterations is chosen, and in each iteration new inputs are resampled for a complete Monte Carlo analysis:

1. Datasets (concentration data, individual data) are resampled from the original database (bootstrap methodology)
2. Parametric inputs, such as portion size uncertainty and processing factors and their variabilities are resampled from parametric distributions.

## 11.1 Resampling datasets

A computer-based instrument to assess the reliability of outcomes is the *bootstrap* (Efron 1979, Efron & Tibshirani 1993). In its most simple, non-parametric form, the bootstrap algorithm resamples a dataset of $n$ observations to obtain a *bootstrap sample* or *resampled set* of again $n$ observations (sampling with replacement, that is: each observation has a probability of $1/n$ to be selected at any position in the new resampled set). By repeating this process $B$ times, one can obtain $B$ resampled sets, which may be considered as alternative data sets that might have been obtained during sampling from the population of interest. Any statistic that can be calculated from the original dataset (*e.g.* the mean, the standard deviation, the 95$^{th}$ percentile, etc.) can also be calculated from each of the $B$ resampled sets. This generates a *uncertainty distribution* for the statistic under consideration. The uncertainty distribution characterises the uncertainty of the inference due to the sampling uncertainty of the original dataset: it shows which statistics could have been obtained if random sampling from the population would have generated another sample than the one actually observed.

In MCRA, two type of data are combined: individual consumption data and concentration data. It makes sense to apply resampling to both type of data separately, in order to characterise the uncertainty in the final intake. In MCRA the uncertainty algorithm (when selected) is applied to:

1. the multivariate consumption patterns and associated body weights: actually the data set of individuals is resampled, and all individual information (consumption patterns for all consumption days, body weight, and age) is coupled to the selected individual.
2. the univariate concentration data sets: these are resampled independently for all foods. In principle, the uncertainty algorithm is applied to the dataset consisting of both non-detects and positive values; in practice, for a dataset with $n_0$ non-detects and $n_1$ positive values, the number of positive values in a resampled set is obtained as a draw from a binomial distribution with parameter $n_1/(n_0 + n_1)$ and binomial total $n_0 + n_1$. Then, this number of values is selected randomnly from the set of $n_1$ positive values.

In MCRA the resulting uncertainty distribution of percentiles of the intake distribution is summarised by specifying empirical 2.5$^{th}$ , 25$^{th}$, 75$^{th}$ and 97.5$^{th}$ percentiles. The outer percentiles constitute a central 95% confidence interval for the variability percentiles. However, for this it is necessary that the number of resampled sets $B$ is high enough. The number of resampled sets should be chosen depending on the confidence level wanted for the uncertainty interval. Typically 500-2000 resampled sets will be reasonable for a 95 % confidence interval (Efron & Tibshirani 1993, pp. 14-15, 275).

The same uncertainty algorithm can also be applied to deterministic estimates which are calculated from data sets. For example the maximum concentration found in a resampled set will be different, if the actual maximum value in the original dataset has *not* been selected. Also data-based estimates of large portion and average body weight will vary.

## 11.2 Resampling parametric distributions, processing

Processing effects are modelled either by a fixed processing factor, or by a lognormal or logistic-normal distribution (depending on the distribution type set in table Processingfactor).
In the former case (fixed factor) the uncertainty distribution is lognormal or logistic-normal with the same mean $\mu$ as the fixed value, and with a standard deviation $\sigma_{unc}$ which is calculated from the specified central; value (procnom) and an estimate of p95 of the uncertainty distribution (procnomuncupp).
The calculation for the logistic-normal distribution (disttype 1):

$$\sigma_{unc} = \{\text{logit(procnomuncupp)} - \text{logit(procnom)}\}/1.645,$$

and for the lognormal distribution (disttype 2).

$$\sigma_{unc} = \{\ln(\text{procnomuncupp}) - \ln(\text{procnom})\}/1.645,$$

Values lower than 0.01 or higher than 0.99 (disttype 1 only) are replaced by default values (0.01 and 0.99); this is useful computationally to avoid problems. In each iteration of the uncertainty analysis a new value is drawn from this distribution to be used as a fixed factor in the Monte Carlo calculation.
In the case of a processing factor distribution (describing the variability of processing factors) two uncertainties can be specified. First, the uncertainty about the central value $\mu$ can be specified as before using a parameter procnomuncupp. Secondly, the uncertainty about the variability standard deviation $\sigma_{var}$ can be specified by the number of degrees of freedom *df* of a modified chi-square distribution which is used to generate new values of $\sigma_{var}$. Setting *df* very high means litte uncertainty, and $\sigma_{var}$ will be almost equal in all iterations of the uncertainty analysis. Setting *df* close to 0 means a large uncertainty, and very different values of $\sigma_{var}$ will be obtained in the iterations of the uncertainty analysis.

# 12 Portion size

A new source of uncertainty may be distinguished by using 24-hour recall methods that quantify consumption using portions size and amounts of portions consumed as the primary measure of consumption. Although individual consumption data are expressed in grams per day, the primary data may be associated with uncertainty in portion size and amount or number of portions consumed. So, the primary data are unitweights (e.g. the weight of a portion shown on a photo, or the weight of a standard household measure) and amounts of units (e.g. the number of shown portions or the number of cups), the multiplication of both values is the amount consumed in grams. The corresponding portion size uncertainty is primarily connected with unitweights and amounts.

## 12.1 Portion size uncertainty

For the European Food Consumption Validation Project (EFCOVAL) the MCRA model for uncertainty is adapted specifically to the six quantification methods of EPIC-SOFT (Table 3).

| Method | Unitweight (*uw*) | Amount (*a*) |
|---|---|---|
| Photographs (P) | Standard portion in grams (Photo 1 of broccoli is 78 g) | Proportion or multiple of standard portion (1 times photo 1 of broccoli) |
| Household measures (H) | Standard portion in grams (a glass of tea is 150 g) | Proportion or multiple of standard portion (2 glasses of tea) |
| Standard units (U) | Standard portion in grams (a can of corn is 285 g) | Proportion or multiple of standard portion (1/2 a can of corn) |
| Standard portion (S) | Standard portion in grams (onion along with fries weighs 10 g) | 1 |
| Gram/volume (G) | 1 | Amount in grams (75 g of potato salad) |
| Unknown (?) | 1 | Amount in grams (Salad dressing weighs 15 grams) |

**Table 3: Overview of EPIC-SOFT quantification methods, with examples in brackets**

Three methods (P, H and U) use both unitweights and amounts, one method (S) uses only unitweights, and two methods (G and ?) use only amounts. The difference between unitweight and amount is as follows: unitweights (in grams) are unique for a specific "food item – quantification method"-combination, but the same for all individuals in the survey, whereas amounts are potentially different for each food item on each eating occasion for each day of an individual. Amounts are in grams (methods G and ?) or in number of units (methods P, H, and U).

Consider a sample of $i = 1,\ldots, N$ individuals for whom dietary intake was measured using 24-hour recalls on *Nday* days ($j = 1\ldots Nday$). Each unique food item that was reported was coded and classified into a food group (e.g., vegetables). The food group of interest consists of $k$ foods ($k = 1\ldots Nfood$). For reasons of clarity, conversion factors that were used (e.g, conversion from raw to cooked) have not been included in the equations below and no uncertainty is attributed to them. To estimate the usual intake distribution of a food group we first calculate $Q_{ij}$, which is defined as the quantity (in grams) of a specific food group that was consumed by individual $i$ on day $j$. Without uncertainty information, these quantities are obtained by summing over all eating occasions $m$ ($m = 1\ldots Nocc_{ij}$) of individual $i$ on day $j$ and over all foods $k$ ($k = 1...Nfood$) belonging to the food group:

$$Q_{ij} = \sum_{k=1}^{Nfood} \sum_{m=1}^{Nocc_{ij}} Q_{ijkm}, \qquad (1)$$

where $Q_{ijkm}$ is the quantity in grams of food $k$ consumed on eating occasion $m$ for individual $i$ on day $j$. For foods which are consumed as single foods, $Q_{ijkm}$ is an amount $a$ (methods G and ?), a unitweight

*uw* (method S), or is calculated by the multiplication of an amount *a* and a unitweight *uw* (methods P, H and U):

$$Q_{ijkm} = a_{ijkm} uw_k \,. \tag{2}$$

For foods which are ingredients in mixed dishes, $Q_{ijkm}$ is calculated as the sum over all relevant mixed dishes *d* ($d = 1,...,Nmix_d$) of the multiplication of the quantity of the mixed dish ($Q_d$) and the proportion of food *k* to the mixed dish ($F_{dk}$):

$$Q_{ijkm} = \sum_{d=1}^{Nmixd} Q_{ijdm} F_{dk} = \sum_{d=1}^{Nmixd} a_{ijdm} uw_d F_{dk} \,, \tag{3}$$

where $a_{ijdm}$ is the amount of the mixed dish and $uw_d$ is the unit weight of the mixed dish.
Both *a* and *uw* are specified for EPIC-SOFT quantification methods P, H, and U, for methods G and ? only *a* is specified and *uw* = 1, and for method S *uw* is specified and *a* = 1.
When interested in the usual intake of nutrients the procedure is basically the same, but now a food group consists of all *Nfood* foods containing the nutrient of interest. The intake of a specific nutrient for individual *i* on day *j* ($I_{ij}$) is then calculated by

$$I_{ij} = \sum_{k=1}^{Nfood} \sum_{m=1}^{Nocc_{ij}} Q_{ijkm} C_k \,, \tag{4}$$

where $C_k$ is the quantity of that nutrient (gram per gram) in food *k*.

## 12.2 Uncertainty analysis

For an uncertainty analysis of the usual intake assessment of foods and nutrients we modelled three sources of uncertainty:

1. sampling uncertainty of the set of individuals interviewed on their consumption,
2. uncertainty in *uw* (for EPIC-SOFT quantification methods P, H, U and S)
3. uncertainty in *a* (for EPIC-SOFT quantification methods G, P, H, U and ?).

In this description of the uncertainty analysis, we focus on the last two uncertainties, both related to the consumed portions. The sampling uncertainty is addressed by bootstrapping the set of individuals.
Both amounts and unit weights are subject to uncertainty. This uncertainty is modelled by lognormal distributions where the mean (m) is the nominal value (i.e. the value used in an analysis without uncertainty), and where a coefficient of variation (*cv*) is specified to describe the amount of uncertainty. In practice a lognormal distribution with mean 1 may be used to generate an uncertainty factor that is multiplied with the nominal value. On a logarithmic scale the lognormal distribution becomes a normal distribution, characterized by two values, usually the mean $\mu$ and the standard deviation $\sigma$. The lognormal distribution can be characterized by specifying $\mu$ and $\sigma$ of the corresponding normal distribution, or, more conveniently, by values on the natural scale (back-transformed). If the natural logarithm (ln) is used then common parameters are $m = exp(\mu + ½ \sigma^2)$ and the coefficient of variation $cv = 100\sqrt{(exp(\sigma^2)-1)}$ (expressed as a percentage).
To assess the uncertainty, values for *a* and *uw* are sampled from the uncertainty distributions (Figure 5) and the usual intake distribution is estimated.

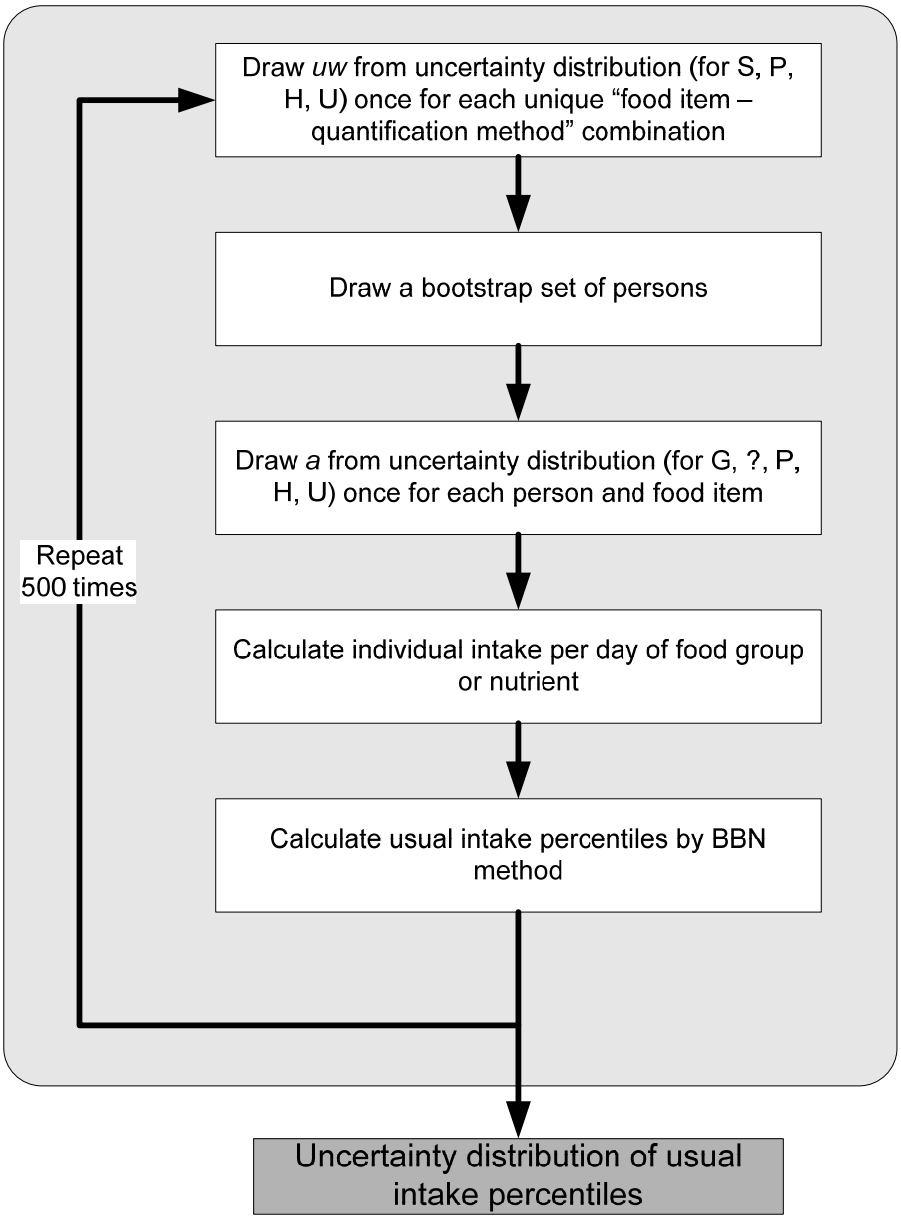



**Figure 5: Flow chart indicating the procedure to quantify the uncertainty due to portion size estimation when conducting 24-hour recall with EPIC-SOFT as well as sampling uncertainty**

This process is repeated in 500 iterations to obtain uncertainty distributions of selected intake percentiles. For *uw* in each iteration one single value for each relevant combination of food and unit is drawn from an uncertainty distribution with $cv_{uw}$. For *a*, values are drawn from an uncertainty distribution with $cv_a$. Here, in each iteration for each food as many values are sampled as there are simulated individuals in the consumption dataset. This is based on the idea that between-individual differences in estimating an amount of a food are far more important than the within-individual variation (across different eating occasions of the same individual). So we ignore the latter variation in estimation quality. To illustrate the difference in the treatment of *uw* and *a*, an example is provided in Table 4 on the consumption of tomatoes of three individuals on two days. In this example individual 1 consumes 1 tomato on day 1, and first 1 and then 2 tomatoes on day 2, etc (see rows labelled 'no uncertainty (nominal)'). In the uncertainty analysis these nominal values (rows labelled ' no uncertainty (nominal)') are modified by factors from a lognormal distribution with mean value 1 (in iterations of the uncertainty analysis, here two iterations are shown labelled 'iteration 1' and 'iteration 2'). In each iteration there is only one uncertainty value for *uw*, but three for *a* (one for each

individual). This example is simplified by *not* resampling the set of individuals; in reality a fresh bootstrap sample from the set of individuals is used in each iteration, and individuals selected more than once receive independent draws for the uncertainty factor for amount.

| | | | day (j) | | | |
|---|---|---|---|---|---|---|
| | | | 1 | | 2 | |
| | individual (i) | eating occasion (m) | unit weight (*uw*) | amount (*a*) | unit weight (*uw*) | amount (*a*) |
| no uncertainty (nominal) | 1 | 1 | 70 | 1 | 70 | 1 |
| | | 2 | - | - | 70 | 2 |
| | 2 | 1 | - | - | 70 | 1.5 |
| | 3 | 1 | 70 | 1 | - | - |
| | | 2 | 70 | 1 | - | - |
| | | 3 | 70 | 0.5 | - | - |
| iteration 1 | 1 | 1 | 70 x 0.98 | 1 x 1.12 | 70 x 0.98 | 1 x 1.12 |
| | | 2 | - | - | 70 x 0.98 | 2 x 1.12 |
| | 2 | 1 | - | - | 70 x 0.98 | 1.5 x 1.10 |
| | 3 | 1 | 70 x 0.98 | 1 x 0.93 | - | - |
| | | 2 | 70 x 0.98 | 1 x 0.93 | - | - |
| | | 3 | 70 x 0.98 | 0.5 x 0.93 | - | - |
| iteration 2 | 1 | 1 | 70 x 1.07 | 1 x 0.88 | 70 x 1.07 | 1 x 0.88 |
| | | 2 | - | - | 70 x 1.07 | 2 x 0.88 |
| | 2 | 1 | - | - | 70 x 1.07 | 1.5 x 1.01 |
| | 3 | 1 | 70 x 1.07 | 1 x 1.14 | | - |
| | | 2 | 70 x 1.07 | 1 x 1.14 | | - |
| | | 3 | 70 x 1.07 | 0.5 x 1.14 | | - |

**Table 4:Example of simulations in an uncertainty of consumption portions**

## 12.3 Specification of portion size uncertainties

For quantification methods P, H and U the uncertainty in *uw* as well as the uncertainty in *a* needs to be specified, for quantification methods G and ? the uncertainty in *a* needs to be specified, and for method S the uncertainty in *uw* needs to be specified (Table 3). The uncertainty *cv* specifications were obtained using limited expert opinion to provide estimated upper values for *a* and *uw*, and equating these to the p97.5 of the (log)normal uncertainty distribution (the best estimates are interpreted as the mean *m*).

The uncertainty *cv* for *a* was based as much as possible on information from studies, reports, publications. The uncertainty *cv* of *uw* was obtained as follows:

1. Photos were considered an ordered series, where the lognormal *cv* was derived from the assumption that the p97.5 of the lognormal uncertainty distribution is equal to the nominal *uw* value of the next photo in the series. For the last photo, the *uw* of the previous picture was set as the p2.5 of the lognormal uncertainty distribution;
2. The *cv* for household measures were generalized from *cvs* taken from a report of Hulshof *et al.* on vegetables;
3. The *cv* for standard units and standard portions were assigned by placing the item into one of four categories, namely: a) ordered series: the same method as for photos was used, b) small uncertainty: the p97.5 of the lognormal uncertainty distribution was set to $x_{small}$ times the nominal value; items that were pre-packed and reported as whole products were placed in this category, c) medium uncertainty: the p97.5 of the lognormal uncertainty distribution was set to $x_{medium}$ times the nominal value; items reported as whole products were in this category, d) large uncertainty: the p97.5 of the lognormal uncertainty distribution was set to $x_{large}$ the nominal value; items that were part of a product or man-made were placed in this category.

# 13 Simulated intake data

Contribution by Paul Goedhart

# 14 About MCRA

MCRA is a result of an ongoing co-operation between RIKILT and Biometris since 1998. RIKILT co-ordinates the Dutch KAP programme (Quality of Agricultural Products) where results of monitoring programs for chemical substances in food are gathered in a national database. RIKILT also has a recipe database to link food codes from the Dutch food consumption table to primary agricultural products. Biometris contributes statistical models and programs for quantitative risk analysis.
Since 2005, the program is extended in collaboration with RIVM to include models similar to those available in the STEM (Statistical Exposure Modeling) software. Since 2010, RIVM has incorporated RIKILT activities in the field of risk assessment of …..??

The current release of MCRA is written in **Microsoft Visual C# .NET 2008**. MCRA is internet-based and can be used by registered users at http://mcra.rivm.nl. It consists of a basic program to do the computations and of additional database selection possibilities implemented in ASP.NET. A R-(D)COM interface is used to connect the application with R, which is running in the background for statistical analyses and graphics (http://cran.r-project.org).

An earlier version of the MCRA program, as well as an implementation of the Monte Carlo method in @Risk (1996), have been described in van der Voet *et al*. (1999), further elaboration was given in de Boer & van der Voet (2000, 2001, 2006), de Boer *et al.* (2009) and van der Voet *et al*. (2001).

This manual covers the current release 7.0 (release 7 version 0) and all future updates starting with the same release number. Major updates of the program, encompassing new or improved facilities will be released with an increased release number and a new manual.

Find more information about the current MCRA release in:
**MCRA 7 Reference Manual**
**MCRA 7 Overview**
**MCRA 7 Data Formats**
**MCRA 7 Examples**
**MCRA 7 On Line Help**

# 15 References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